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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/630,626	07/30/2003	Gregory A. Demopulos	PH.1.0037.US2	9065

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EXAMINER	
ALSTRUM ACEVEDO, JAMES HENRY	

ART UNIT	PAPER NUMBER
1616	

MAIL DATE	DELIVERY MODE
08/29/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/630,626	DEMOPULOS ET AL.	
	Examiner	Art Unit	
	James H. Alstrum-Acevedo	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 June 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16 and 18-28* is/are pending in the application.

4a) Of the above claim(s) *4-5, 9, 18, 20, 22, 25, and 27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,6-8,10-16,19,21,23,26,28,55 and 56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/21/007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-16, 18-28, and 55-56 are pending. Applicants have amended claims 55-56. Previously, Applicants cancelled claims 29-54. Applicants have newly cancelled claim 17. Applicants have amended claims 55-56. **Claims 1-3, 6-8, 10-16, 19, 21, 23, 26, 28, and 55-56 are under consideration in the instant office action.** Claims 4-5, 9, 18, 20, 22, 25, and 27 are withdrawn from consideration as being drawn to a non-elected species. Receipt and consideration of Applicants' amended claim set, new IDS (submitted 5/21/2007), and remarks/arguments submitted on June 11, 2007 are acknowledged.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claims 1-3, 6-8, 10-16, 19, 21, 23, 26, 28, and 55-56 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inhibition of pain, effecting mydriasis, and/or decreasing the intraocular pressure during an ophthalmologic procedure, does not reasonably provide enablement for treating or inhibiting inflammation generally **is withdrawn** per Applicants' claim amendments limiting said claims to the inhibition of ocular inflammation.

Response to Arguments

Applicant's arguments, see page 7, filed June 11, 2007, with respect to the rejection of claims 1-3, 6-8, 10-16, 19, 21, 23, 26, 28, and 55-56 under 35 U.S.C. 112, first paragraph (scope of enablement, see office action mailed March 7, 2007) have been fully considered and are persuasive. The rejection of claims 1-3, 6-8, 10-16, 19, 21, 23, 26, 28, and 55-56 under 35 U.S.C. 112, first paragraph (scope of enablement) has been withdrawn.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Applicant Claims
2. Determining the scope and contents of the prior art.
3. Ascertaining the differences between the prior art and the claims at issue; and resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3, 6-8, 10-16, 19, 21, 23, 26, 28, and 55-56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gan (U.S. Patent No. 5,523,316) in view of Arshinoff et al. ("Pharmacotherapy of photorefractive keratectomy," *J. Cataract Refract. Surg.* 1996, *22*, pp 1037-1044; New IDS reference) and Revision of Pharmacology ("ROP"; 1/3/2007 IDS reference).

Applicant Claims

Applicants claim a method for perioperatively inhibiting ocular inflammation, inhibiting pain, effecting mydriasis, and/or decreasing intraocular pressure (IOP) during an ophthalmologic procedure comprising continuously irrigating ocular tissues during an ophthalmologic procedure with a solution including at least (a) first agent and (b) second agent, wherein each agent is selected to act on a plurality of differing molecular targets and is selected from physiological classes of (i) anti-inflammatory agents, (ii) analgesic agents, (iii) mydriatic agents, and (iv) agents for decreasing IOP, the 2nd agent providing at least one physiologic function different than a function or functions provided by the 1st agent, wherein at least one of the 1st and 2nd agents is a mydriatic agent (e.g.alpha-1 adrenergic receptor agonists, such as phenylephrine, or anticholinergic agents, such as atropine) or an IOP reducing agent (e.g. beta adrenergic receptor

antagonist, such as timolol; carbonic anhydrase inhibitors, such as brinzolamide; or alpha -2 adrenergic agonist, such as oxymetazoline).

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

The teachings of Gan were set forth on pages 4-5 of the office action mailed on June 1, 2006. Additional relevant teachings of Gan are set forth herein. The art recognizes that desirability that irrigation solutions utilized in ophthalmologic procedures emulate the contents and properties of the aqueous humor (col. 3, line 64 through col. 4, line 1). Thus, suitable irrigation solutions provide the eye with an energy source (e.g. glucose), a proper pH environment (i.e. pH of about 7.4) through a phosphate/bicarbonate buffer system, and metabolic support via the presence of necessary electrolytes, such as **sodium, magnesium, calcium, and potassium cations and chloride anions** (col. 2, line 31 through col. 3, line 4; col. 8, lines 23-57; claims 1, 10, 21, 30-40). The presence of glutathione is also desirable as it aids in aiding the metabolic pump mechanism (col. 2, line 67 through col. 3, line 4; col. 7, line 67 through col. 8, line 3). Glutathione is an antioxidant and its presence helps protect corneal endothelial cells from photochemically generated active oxygen. The formation of active oxygen (i.e. oxygen radicals) is associated with long exposure to light, such as occurs during cataract surgery or other intraocular surgical procedures, and active oxygen may damage ocular tissue. **The art recognizes that elevation of intraocular pressure (IOP) can damage the optic nerve**, which may result from surgical trauma, and thus, **it is desirable to prevent or minimize deleterious changes of the IOP (col. 4, lines 2-13, 40-47)**. **Beta-blockers and alpha-adrenergic agonists are known to have utility in controlling the IOP** (col. 5, lines 15-21). Preferred beta-blockers

for controlling IOP include **timolol, levobunolol, and mertipranolol** (col. 5, lines 22-67, especially lines 65-67) and these are present in amounts ranging from **0.001-0.1% w/w** based on the weight of the total composition. Preferred alpha-adrenergic agonists are clonidine derivatives, as described by formula (II) in Gan (col. 6, lines 17 through col. 7, line 23), and other clonidine-like compounds (col. 7, lines 23-46), wherein said alpha-adrenergic agonists are present in an amount of about 0.001-0.1 % w/w (col. 7, lines 47-49).

Arshinoff teaches that the principal pharmacologic agents that have been reported to be useful perioperatively for photorefractive keratectomy (PRK) include **topical anesthetics, antibiotics, anti-inflammatory glucocorticoids, and nonsteroidal anti-inflammatories (NSAIDs)** (paragraph bridging pages 1037-1038). Specific examples of these principal pharmacologic agents utilized in PRK are given in Table 2 on page 1039. Regarding the treatment of pain associated with PRK, the art has reported that topical **diclofenac or ketorolac (i.e. an NSAID) with homoatropine (i.e. a mydriatic agent)** and a soft bandage was **the most effective regimen for post-PRK pain** (paragraph bridging left and right columns on page 1041). To prevent subepithelial infiltrative keratitis **it is recommended to concurrently administer NSAIDs and topical steroids (i.e. known anti-inflammatories)** with a bandage soft contact lens (pg. 1043, conclusion, 2nd paragraph).

The ROP generally teaches the topical and systemic drugs utilized routinely in the diagnosis and treatment of ocular diseases in the field of ophthalmology (pg. 25). Several types of drugs are used in ophthalmology to prevent or reduce inflammation, such as corticosteroids, which are widely used and typically administered locally (pg. 28). NSAIDs are used (i) to **manage inflammatory conditions, including scleritis and episcleritis, (ii) inhibit**

intraoperatirve miosis during cataract surgery, (iii) pain in epithelial corneal defects after PRK, and (iv) in the prophylaxis and reduction of anterior segment inflammation following surgery and argon laser trabeculoplasty (pg. 29, left column). Other anti-inflammatories that are used include vasoconstrictors, such as xylometazoline and **phenylephrine**, which may also cause mydriasis and lower IOP when used at higher concentrations (pg. 29, right column).

Ascertainment of the Difference Between Scope the Prior Art and the Claims

(MPEP §2141.012)

Gan does not expressly teach continuous irrigation or the use of irrigating solutions comprising analgesics or anti-inflammatories. These deficiencies are obvious per the teachings of Gan or are cured by the teachings of Arshinoff and the ROP.

Finding of Prima Facie Obviousness Rational and Motivation
(MPEP §2142-2143)

It would have been prima facie obvious to combine the teachings of Gan, Arshinoff, and the ROP, because all references are in the same field of endeavor, namely the field of ophthalmologic surgical procedures and materials. From the teachings of Gan it would have been apparent to an ordinary skilled artisan at the time of the instant invention that one would want to provide an irrigation solution comprising electrolytes, an energy source, antioxidants, and IOP reducing agents to prevent or at least minimize the likelihood of changes in the IOP that could lead to ocular damage. It would have been prima facie obvious to combine the teachings of Gan and Arshinoff, because the prior art recognizes that although the combination of steroids and NSAIDs is effective in the prophylaxis of subepithelial keratitis, steroids are known to cause

undesirable changes to IOP. Thus, the inclusion of Gan's invented irrigation solution and methods would allow an ordinary skilled artisan to control IOP with a reasonable expectation of success. Regarding the relative amount of a given drug present in an irrigation solution, it is well within the skill of an ordinary artisan to ascertain the therapeutically effective quantity of a known drug or drugs for use to treat conditions for which said drugs are routinely indicated. Regarding continuous irrigation, it would have been prima facie obvious to a person of ordinary skill in the art to apply an irrigation solution continuously, because such an application would be reasonably expected to emulate the action of the naturally occurring aqueous humor during an ophthalmologic procedure and in addition it would be reasonably expected to remove any ambient particulate matter, such as dust, from settling upon the eye. The use of drugs in an irrigation solution in a manner for which said drugs are routinely used in ophthalmologic procedures is prima facie obvious and such use would provide an ordinary skilled artisan with a reasonable expectation of success due to the predictable nature of said use. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference

claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1 and 28 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over (1) claims 1-12 and 18 of U.S. Patent No. 6,261,279 (USPN '279); (2) claims 18-20 of U.S. Patent No. 6,413,961 (USPN '961); and (3) claims 12-17 and 23-28 of U.S. Patent No. 6,420,432 (USPN '432) all in view of Gan (U.S. Patent No. 5,523,316), Arshinoff et al. (*J. Cataract Refract. Surg.* 1996, *22*, pp 1037-1044), and Revision of Pharmacology ("ROP"; Revision of Pharmacology) for the reasons of record set forth on pages 12-13 of the office action mailed on June 1, 2006 and further articulate below. The cited U.S. Patents lack the express teaching of methods wherein at least one agent is a mydriatic agent or an intraocular pressure-increasing agent. This deficiency is cured by the teachings of Gan, Arshinoff, and ROP, which have been set forth above in the instant office action and/or on pages 4-5 of the office action mailed on June 1, 2006. Gan clearly teaches the desirability of including IOP reducing agents in an irrigation solution utilized in an ophthalmologic surgical procedure, as evidenced by the art's recognition that an increase in ocular pressure can lead to irreversible damage to the optical nerve. The prior art has also recognized that the application of a NSAID (e.g. ketorolac) in combination with a mydriatic agent (e.g. homoatropine) is effective to treat

pain associated with ophthalmologic procedures, such as PKR. Thus, it would have been prima facie obvious to an ordinary skilled artisan that the application of an irrigation solution comprising an NSAID, a steroid, result in mydriasis when applied directly to ocular tissues, such as in claims 1 and 28 of the instant application. For these reasons, an ordinary skilled artisan would conclude that claims 1 and 28 of the instant application are *prima facie* obvious over the cited claims of USPN '279, USPN '961, and USPN '432.

Conclusion

Claims 1-3, 6-8, 10-16, 19, 21, 23, 26, 28, and 55-56 are rejected. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James H. Alstrum-Acevedo whose telephone number is (571) 272-5548. The examiner can normally be reached on M-F, 9:00-6:30, with every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on (571) 272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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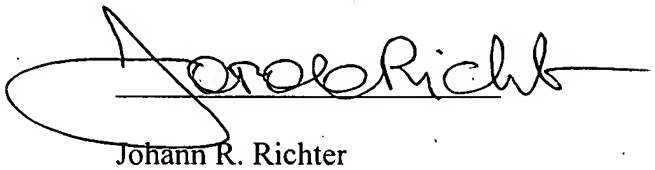

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